Exhibit IND11

Exhibit F

[To N. Bryan's Opening Expert Report]

Original article

Effects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial

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Abstract. *Purpose:* Quantitative measurement of tracer uptake in a tumour can be influenced by a number of factors, including the method of defining regions of interest (ROIs) and the reconstruction parameters used. The main purpose of this study was to determine the effects of different ROI methods on quantitative outcome, using two reconstruction methods and the standard uptake value (SUV) as a simple quantitative measure of FDG uptake. *Methods:* Four commonly used methods of ROI definition (manual placement, fixed dimensions, threshold based and maximum pixel value) were used to calculate SUV ($SUV_{[MAN]}$, $SUV_{15\ mm}$, SUV_{50}, SUV_{75} and SUV_{max}, respectively) and to generate "metabolic" tumour volumes. Test–retest reproducibility of SUVs and of "metabolic" tumour volumes and the applicability of ROI methods during chemotherapy were assessed. In addition, SUVs calculated on ordered subsets expectation maximisation (OSEM) and filtered back-projection (FBP) images were compared. *Results:* ROI definition had a direct effect on quantitative outcome. On average, $SUV_{[MAN]}$, $SUV_{15\ mm}$, SUV_{50} and SUV_{75}, were respectively 48%, 27%, 34% and 15% lower than SUV_{max} when calculated on OSEM images. No statistically significant differences were found between SUVs calculated on OSEM and FBP reconstructed images. Highest reproducibility was found for $SUV_{15\ mm}$ and $SUV_{[MAN]}$ (ICC 0.95 and 0.94, respectively) and for "metabolic" volumes measured with the manual and 50% threshold ROIs (ICC 0.99 for both). Manual, 75% threshold and maximum pixel ROIs could be used throughout therapy, regardless of changes in tumour uptake or geometry. SUVs showed the same trend in relative change in FDG uptake after chemotherapy, irrespective of the ROI method used. *Conclusion:* The method of ROI definition has a direct influence on quantitative outcome. In terms of simplicity, user-independence, reproducibility and general applicability the threshold-based and fixed dimension methods are the best ROI methods. Threshold methods are in addition relatively independent of changes in size and geometry, however, and may therefore be more suitable for response monitoring purposes.

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Introduction

Positron emission tomography (PET) is one of the fastest growing (nuclear) imaging modalities. Depending on the purpose, e.g. clinical management or research, either visual assessment of PET images will suffice or quantitative measurement of tracer uptake will be needed. The latter case requires definition of a region or volume of interest (ROI or VOI), wherein measured tracer uptake is determined.

A survey of the literature over the past 10 years on the quantitative use of ^{18}F-fluoro-deoxy-glucose (FDG) reveals a wide variety of methods for ROI definition. These include manual placement of ROIs covering the whole tumour using either average counts or maximum pixel value [1–3], placement of ROIs with fixed dimensions around the "hottest" area within a tumour [4–8] and the use of isocount contour ROIs with thresholds varying from 50% to 95% of the maximum pixel value [9–13]. Reasons for adopting a certain ROI strategy are usually of a practical nature (simplicity, relative insensitivity to partial volume effects, etc.), although different views on the biological significance of measuring maximum versus average tumour activity may also play a role. To date, only a limited number of studies have addressed reproducibility of methods of ROI definition [10, 14, 15]. It is

clear that the method of ROI definition will affect quantitative measurements of tracer uptake. Furthermore, as iterative reconstruction algorithms are increasingly used in addition to or instead of filtered back-projection (FBP), this too will have an impact on ROI definition and quantitative outcome [16, 17]. Finally, a recent comprehensive phantom and simulation study [18] has shown a strong and direct dependency of SUV on image resolution, noise and ROI methodology, findings that warrant further investigation in a clinical setting.

In view of the methodological variability, the main purpose of this study was to determine the effects of different ROI methods on quantitative outcome, using two reconstruction methods and the standard uptake value (SUV) as a simple quantitative measure of FDG uptake. For several commonly used methods of ROI definition, test–retest reproducibility of SUV and of the generated ROI volumes was calculated. Furthermore, applicability of ROI methods and appropriateness for use in a response monitoring trial were assessed.

Materials and methods

Patients

Eleven patients (nine men, two women, age 52±7 years) with stage IIIb and IV non-small cell lung cancer were scanned twice on two consecutive days before receiving any treatment [19].

Sixteen female patients (age 51±8 years) with locally advanced breast cancer or stage IV breast cancer were scanned before treatment, and additionally after one, three and six courses of chemotherapy. All primary tumours had previously been diagnosed by histology or cytology. All patients were scanned as part of ongoing trials, which were approved by the Medical Ethics Committee of the VU University Medical Centre and for which informed consent was obtained.

PET imaging

The PET scanner (ECAT EXACT HR+; Siemens/CTI, Knoxville) used provides an axial field of view of 15.5 cm and produces 63 transaxial slices with a slice thickness of 2.5 mm.

All patients had fasted for at least 6 h prior to scanning. Patients were studied in the supine position with the arms at their sides. They were positioned in such a way that the dominant lesions were in the centre of the field of view. The distance between the suprasternal notch and the upper field of view (laser beam alignment) was recorded and used on subsequent scans. First, a 10-min transmission scan was acquired using three rotating ^{68}Ge rod sources; this was followed by intravenous injection of a bolus of approximately 370 MBq FDG, simultaneously starting a dynamic emission scan in 2D mode. Data acquisition (6×5, 6×10, 3×20, 5×30, 5×60, 8×150, 6×300 s frames) was identical for all scans.

Reconstruction parameters

Emission data were corrected for decay, dead time, scatter, random coincidences and measured photon attenuation. Scans were reconstructed into 128×128 matrices using both FBP with a 0.5 Hanning filter and ordered subsets expectation maximisation (OSEM, two iterations with 16 subsets), followed by post-smoothing with a 0.5 Hanning filter. The resulting transaxial spatial resolution for both reconstruction methods was ~7 mm full-width at half-maximum at the centre of the field of view. Resolution matching is a prerequisite before different reconstruction algorithms can be compared [20].

Region of interest definition

ROIs were defined on sum images of the last three frames (i.e. 45–60 min p.i.) as follows:

1. ROIs were drawn manually on consecutive transaxial slices around the entire lesion (tumour, node or metastasis) and were then grouped to yield VOIs.
2. The single maximum pixel value within the manually drawn VOIs was selected.
3. Circular 15-mm-diameter ROIs were drawn semi-automatically over the area of maximum FDG uptake in a lesion and in one slice above and beneath, and the three slices were grouped into VOIs.
4. VOIs were generated automatically using a region growing method, which only included pixels greater than a preset threshold, in this study 50% and 75% of the maximum value within a lesion.

SUV calculations

SUV was corrected for lean body mass (LBM) and for plasma glucose (C_{glu}) as described elsewhere [21]. SUVs were calculated using the average counts and the single maximum pixel count within the manually defined ROIs ($SUV_{[MAN]}$ and SUV_{max}, respectively), using the average counts within the 15-mm ROIs ($SUV_{15\ mm}$), and using the average counts within the threshold-defined ROIs (SUV_{50} and SUV_{75}). All SUVs were calculated for both FBP and OSEM reconstructed images ($SUV_{[FBP]}$ and $SUV_{[OSEM]}$, respectively).

Statistics

In the lung cancer group, test–retest reproducibility was tested by calculating intraclass correlation coefficients (ICCs), the mean difference and the mean percentage (%) difference for individual SUV measurements and ROI volume measurements. For the ICC, the model was used that assumes random observers performing a single measurement on a group of subjects. The mean % difference was used to assess the intra-subject variability of the measured SUVs and was calculated as follows: (SUV on day 1−SUV on day 2)/mean of SUV1 and SUV2.

In the breast cancer group, relative changes in SUVs, as measured with various ROI methods during chemotherapy, were compared using multilevel analysis. Thus it was taken into account that both the different SUVs and the relative changes over time during chemotherapy are correlated within a patient. In the multilevel analysis, three levels were considered: (1) different SUVs, (2) measurements over time and (3) patients. When a significant interaction with time was found, this implied that the two methods differed significantly in the relative change measured over time during chemotherapy.

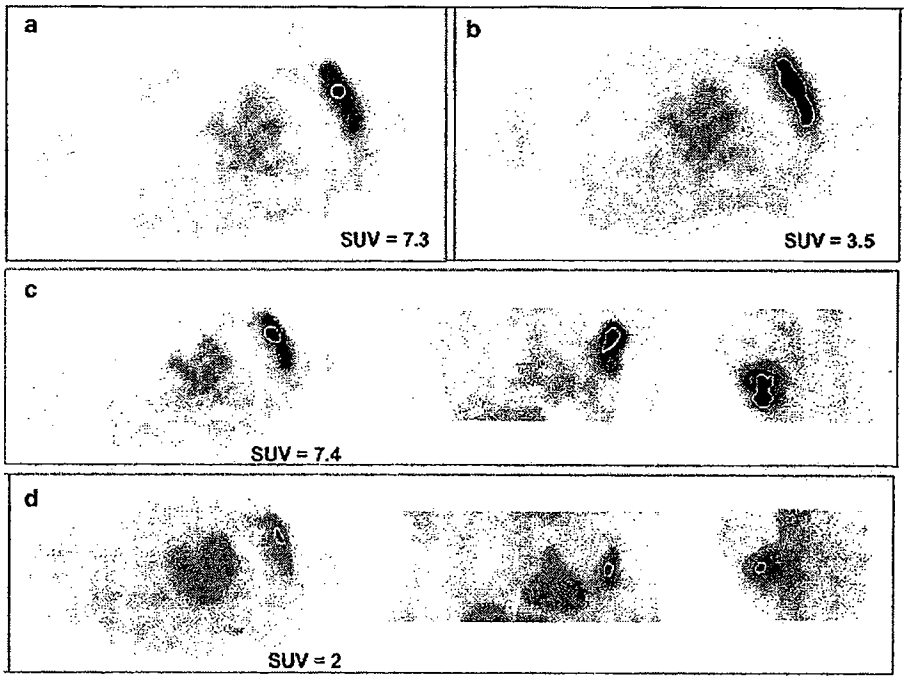

Fig. 1a–d. Different ROI definition methods in a breast cancer patient, OSEM images. **a** Transaxial slice, 15-mm ROI; baseline. **b** Transaxial slice, manual ROI; baseline. **c, d** Transaxial, coronal and sagittal slices, 3D-region growing method (75% threshold); baseline and after six courses of chemotherapy, respectively

Results

Applicability of ROI definition methods

Forty-six lesions (17 primary breast cancers, 12 primary lung tumours, 2 infraclavicular, 10 mediastinal and 5 axillary lymph nodes) were defined on the baseline PET scans of the breast cancer and lung cancer patients. Patient characteristics are listed in Table 1. Lesions were generally large and had a skewed distribution with a mean (± standard deviation, SD) "metabolic" tumour volume (manual ROI method) of 23.7±36.1 cm^3 (median 8.7 cm^3; interquartile range, IQR, 3.6–15.8 cm^3) on day 1 and 25.3±38.9 cm^3 (median 8.9 cm^3; IQR 3.3–14.6 cm^3) on the second day.

OSEM reconstructed scans were better suited for ROI definition than FBP reconstructed images, both at baseline and after chemotherapy. With FBP, ROI definition became impossible in most cases after more than one course of chemotherapy because of poor image quality and/or streak artefacts. Therefore, for $SUV_{[FBP]}$ calculations, the ROIs drawn on the OSEM images were projected onto the FBP images.

The maximum pixel, manual and 75% threshold methods were always applicable on OSEM reconstructed images, both at baseline and after chemotherapy. Because most lesions were large, the 15-mm method ROIs could almost always be used except in one baseline lymph node metastasis with a diameter of 12 mm. With the 50% threshold, an increasing number of ROIs had to be discarded after chemotherapy because non-tumour tissue was also included in the ROI (i.e. tissue was included that was outside the perceived boundaries of the tumour or ROIs were unrealistically large). Because of this, the 50% threshold method was not included in the statistical analyses after baseline. See Fig. 1 for examples of different ROI methods applied to the same tumour.

Table 1. Patient characteristics

Parameter	Value
No. of patients	27
Sex (F/M)	18/9
Age ± SD (range)	
Lung cancer patients	52±6.8 yr (45–65 yr)
Breast cancer patients	51±8.2 yr (35–63 yr)
Clinical stage (*n*)	
LABC	8
Stage IV breast cancer	8
Stage IIIB NSCLC	3
Stage IV NSCLC	8
Tumour localisation (*n*)	
Breast	17[a]
Lung	12[a]
Axilla[b]	5
Mediastinum[b]	10
Infraclavicular[b]	2
No. of lesions	46

SD, standard deviation; LABC, locally advanced breast cancer; NSCLC, non-small cell lung cancer

[a] Multifocal cancer

[b] All lung cancer metastases.

Table 2. Test–retest reproducibility of SUV and ROI volume using different methods of ROI definition in lung cancer patients

ROI method	*N*	Scan 1	Scan 2	Mean difference	Mean % difference	ICC
$SUV_{[OSEM]}$						
Manual	29	5.04±1.49	5.00±1.65	0.04±0.56	9%±8%	0.94
15 mm	28[a]	6.69±2.54	6.62±2.60	0.07±0.83	10%±8%	0.95
50% threshold	28[a]	6.22±1.91	6.08±2.15	0.14±0.85	12%±11%	0.91
75% threshold	29	7.89±2.49	7.69±2.76	0.20±1.23	14%±13%	0.89
Maximum pixel	29	9.22±2.96	8.97±3.31	0.25±1.33	13%±12%	0.91
$SUV_{[FBP]}$						
Manual	29	5.16±1.45	5.11±1.60	0.05±0.53	8%±8%	0.94
15 mm	28[a]	6.71±2.39	6.62±2.40	0.09±0.79	8%±7%	0.95
50% threshold	28[a]	6.35±1.80	6.19±1.99	0.16±0.81	13%±13%	0.91
75% threshold	29	7.86±2.25	7.66±2.42	0.20±1.04	12%±10%	0.90
Maximum pixel	29	9.32±2.61	9.09±2.86	0.23±1.34	13%±11%	0.88
ROI volume (cm^3)						
Manual	29	23.67±36.09	25.25±38.89	-1.58±4.64	20%±15%	0.99
50% threshold	28[a]	12.97±22.19	12.97±21.64	0.01±2.83	23%±20%	0.99
75% threshold	29	2.39±3.95	2.57±5.34	-0.19±2.34	55%±35%	0.88

N, number of ROI lesions; ICC, intraclass correlation coefficient
[a] One ROI discarded because non-tumour tissue was also included

Test–retest data: lung cancer patients

Table 2 shows test–retest characteristics of SUVs for various ROIs. Differences between SUVs calculated on two consecutive days were not statistically significant. ICCs of repeat measurements varied between 0.88 for SUV_{max} and 0.95 for $SUV_{15\ mm}$. Smallest mean difference and mean percentage difference were found for SUVs based on manual and 15-mm ROIs. Reproducibility of "metabolic" tumour volumes measured on consecutive days was excellent for manual and 50% threshold tumour ROIs (the 15-mm and maximum pixel "metabolic" tumour volumes were obviously excluded).

Influence of reconstruction method on quantitative outcome

No significant differences were observed between (identical) baseline SUVs measured on OSEM and on FBP images (Table 2). ICCs for baseline $SUV_{[OSEM]}$ and $SUV_{[FBP]}$ values were 0.98 (SUV_{max}), 0.99 (SUV_{75}) and 1.00 (SUV_{50}, $SUV_{15\ mm}$ and $SUV_{[MAN]}$) for lung and breast cancer lesions combined.

To further investigate the behaviour of $SUV_{[OSEM]}$ and $SUV_{[FBP]}$ over a wide range of SUV values, the ratios of SUV_{max}, SUV_{75}, $SUV_{[MAN]}$ and $SUV_{15\ mm}$ to SUV_{50} were plotted against SUV_{50}, which was arbitrarily chosen as the "reference" in this case (Fig. 2). Ratios (±SD) of SUV_{max}, SUV_{75}, $SUV_{[MAN]}$ and $SUV_{15\ mm}$ to SUV_{50} calculated on the OSEM images were 1.51±0.06, 1.29±0.06, 0.79±0.17 and 1.11±0.13, respectively (Table 3). For FBP reconstructed images, comparable ratios were found for SUV_{75}, $SUV_{[MAN]}$ and $SUV_{15\ mm}$. The ratio (±SD) of SUV_{max} to SUV_{50}, however, demonstrated an increasingly positive bias when calculated on FBP images for very low SUVs (compare Fig. 2a with Fig. 2b). This tendency to overestimate lower SUV values was only seen with SUV_{max} and only on FBP images (Fig. 2c). $SUV_{[MAN]}$, $SUV_{15\ mm}$, SUV_{50} and SUV_{75} were on average 48%, 27%, 34% and 15% lower than SUV_{max} (OSEM images, Table 3).

Table 3. Ratio of various SUV values at baseline (lung and breast lesions combined)

Ratio	Mean±SD (range)
OSEM	
$SUV_{[MAN]}/SUV_{50}$	0.79±0.17 (0.39–1.06)
$SUV_{15\ mm}/SUV_{50}$	1.11±0.13 (0.79–1.40)
SUV_{75}/SUV_{50}	1.29±0.06 (1.07–1.43)
SUV_{max}/SUV_{50}	1.51±0.06 (1.27–1.63)
FBP	
$SUV_{[MAN]}/SUV_{50}$	0.79±0.16 (0.42–1.08)
$SUV_{15\ mm}/SUV_{50}$	1.09±0.13 (0.76–1.39)
SUV_{75}/SUV_{50}	1.26±0.06 (1.13–1.37)
SUV_{max}/SUV_{50}	1.55±0.18 (1.33–2.15)
OSEM	
$SUV_{[MAN]}/SUV_{max}$	0.52±0.11 (0.27–0.71)
$SUV_{15\ mm}/SUV_{max}$	0.73±0.08 (0.55–0.89)
SUV_{75}/SUV_{max}	0.66±0.03 (0.62–0.79)
SUV_{50}/SUV_{max}	0.85±0.02 (0.81–0.92)

SD, standard deviation

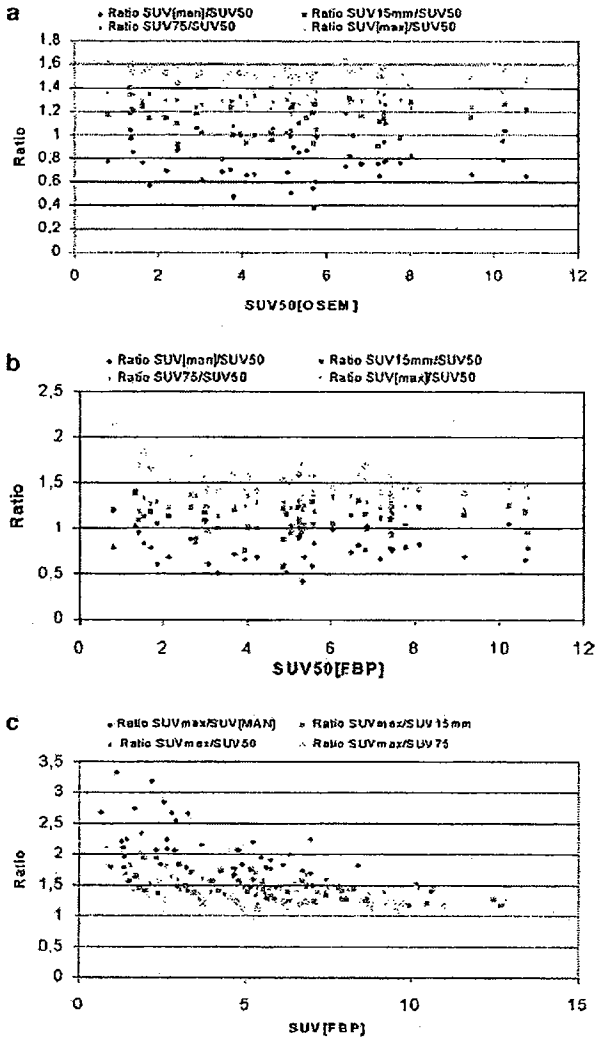

Fig. 2a–c. Ratios of $SUV_{[MAN]}/SUV_{50}$, $SUV_{15\ mm}/SUV_{50}$, SUV_{75}/SUV_{50} and SUV_{max}/SUV_{50} plotted against SUV_{50} values, calculated on **a** OSEM and **b** FBP reconstructed images. **c** Ratios of $SUV_{max}/SUV_{[MAN]}$, SUV_{max}/SUV_{50}, $SUV_{max}/SUV_{15\ mm}$ and SUV_{max}/SUV_{75} calculated on FBP reconstructed images. Breast and lung cancer lesions at baseline (n=46)

Relative changes in FDG uptake during chemotherapy

Figure 3 illustrates the averaged relative SUV changes measured after one, three and six courses of chemotherapy in 16 breast cancer patients using various ROI methods. Analysing the overall trend in measured change in FDG uptake, observed changes were consistently lower when measured with $SUV_{[MAN]}$, but differences were only significant in comparison with $SUV_{15\ mm}$ (multilevel analysis, $p<0.05$). Relative changes measured with $SUV_{15\ mm}$, SUV_{75} and SUV_{max} were similar.

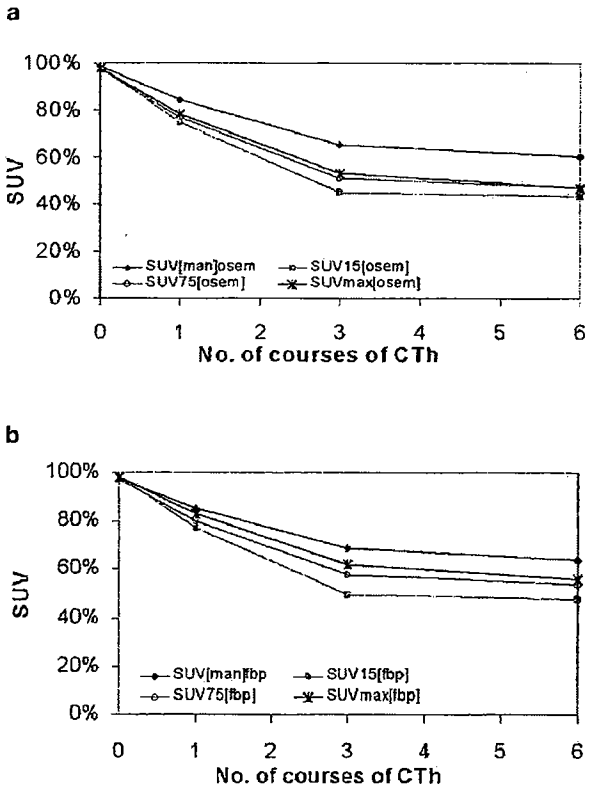

Fig. 3a, b. Average relative changes in $SUV_{[MAN]}$, $SUV_{15\ mm}$, SUV_{75} and SUV_{max} measured in 16 breast cancer patients after one, three and six courses of chemotherapy (*CTh*) on OSEM (**a**) and FBP (**b**) reconstructed images

Discussion

When SUVs are to be used for diagnostic purposes, e.g. to differentiate benign from malignant lesions [1, 22, 23], it is important to realise that ROI definition has a direct influence on the quantitative outcome. For example, in comparison with the maximum pixel value, SUV may be more than 50% lower when a manual ROI is used [10, 16]. In the present study, $SUV_{[OSEM]}$ values were 48%, 27%, 34% and 15% lower in comparison with SUV_{max} when manual, 15 mm, 50% and 75% threshold ROIs were used, respectively. Reported cut-off values for SUVs are therefore not generally applicable when ROI methodology differs.

Test–retest reproducibility was highest for $SUV_{15\ mm}$ and $SUV_{[MAN]}$. This is directly related to the use of fixed dimensions (which by definition do not vary) and to the fact that the same observer drew the regions, respectively. SUV_{max} calculations were least reproducible. The mean % differences and the ICCs of SUVs in this study were comparable with values reported in three previous studies on test–retest reproducibility [15, 24, 25], although slightly lower. This can be explained by differ-

ences in statistical methodology and in the lesions selected for ROI drawing. For example, for SUV_{max}, using only primary lung tumours, like Nakamoto et al. [15] and Minn et al. [24] did, and not lymph node metastases as well, would have resulted in a mean % difference ± SD of 11%±8% in our study population, which is very similar to their results (data not shown). Similarly, the model used to calculate an ICC makes a difference, e.g. the ICC of SUV_{max} could increase from 0.91 to 0.95, depending on which assumptions are used in the calculation of the ICC.

The ROI methods used in this study represent commonly used definition methods (manual, fixed dimensions, threshold based and maximum pixel value). Ideally, a method for ROI definition should be simple, reproducible, automatic, generally applicable, user-independent and relatively insensitive to partial volume effects. In a response monitoring setting, it is also important whether the aim is to measure overall response in a (large or small) volume which remains fixed, regardless of actual change in tumour dimensions, or to measure response in the metabolically most active part of the tumour only. The question as to which approach gives the best indication of tumour response has not yet been resolved.

The fixed dimension method is simple, (semi-)automatic and presumably less sensitive to partial volume effects, if tumour size changes during therapy, than ROIs that encompass the entire tumour [5]. In response monitoring studies where fixed dimension ROIs have been used, however, lesions were usually large and/or lesion evaluation usually stopped after one or two courses of therapy [5–8] and only rarely after three or more courses [26, 27]. In the latter study [27] the authors made note of the potential problems of using a fixed ROI, deriving from the fact that the size and shape of tumours change substantially during therapy. In addition, in a recent simulation study [18], 15-mm ROIs showed the largest underestimation of true activity in comparison with other tested ROI methods, especially for the smallest lesions (≤2 cm). This method obviously can be used only if lesions either are or remain larger than ±2 cm (in the axial field of view), otherwise recovered counts will be underestimated.

Threshold methods are also simple and user-independent and recovered counts are relatively independent of lesion size [10] and of changes in geometry. Provided that tumour size remains larger than twice the image resolution and tumour uptake remains higher than the background, this method is very suitable for response monitoring purposes, in particular because its application is independent of changes in tumour geometry (Fig. 1c,d). It is worth contemplating whether thresholds should be set lower to sample a larger part of the tumour or higher to pinpoint the metabolically most active part of a tumour. Based on the higher reproducibility, the 50% threshold method would have been a better candidate for response monitoring than the 75% threshold, but it proved to be unsuitable in many cases after therapy, because non-tumour tissue was also included in the ROI. This is a problem which can probably be solved by using a so-called background-corrected 50% threshold method, i.e. a threshold set halfway between the background activity and the maximum pixel [18, 28], instead of at 50% of the maximum pixel regardless of background activity.

An advantage of threshold methods is that they can also be used to assess "metabolic" tumour volume [29, 30]. In the present study, tumour volumes had a left-skewed distribution. Test–retest reproducibility of measured "metabolic" tumour volume has, to the best of our knowledge, not been reported before. Reproducibility was much higher for the 50% threshold than for the 75% threshold (ICC 0.99 vs 0.88). Measuring changes in "metabolic" tumour volume might be a valuable additional tool to characterise tumour response.

The maximum pixel method is often used because of its insensitivity to partial volume effects and to avoid inclusion of necrotic or other non-tumour elements [31]. However, SUV_{max} had the lowest reproducibility in this study and showed an increasing positive bias in comparison with other SUV methods on FBP images with low tumour uptake (Fig. 2b,c). Moreover, use of the maximum pixel does not necessarily eliminate the dependency of measured activity on tumour size [18].

The manual ROI method was included for completeness, but has numerous disadvantages, despite the high reproducibility found in this study: it is user-dependent, laborious and, if averaged recovered counts are used, highly sensitive to partial volume effects [32].

Finally, it is important to note that despite the different characteristics of the ROI methods, changes in SUV measured during chemotherapy were similar in trend, regardless of the method used (Fig. 3).

One of the objectives of this study was to compare the influence of OSEM and FBP reconstruction on SUV outcome. Most studies with a similar objective have compared OSEM and segmented attenuation correction (SAC) with FBP and measured attenuation (MAC). Significantly higher values for OSEM-SAC SUVs were found [17, 33, 34], but two of these studies attributed these differences to the use of different reconstruction filters [33, 34]. Two studies compared OSEM-MAC with FBP-MAC. One included oncology patients (various malignancies) and found similar SUVs except in the pelvic area [35]. The other included HIV patients with multiple lymph node abnormalities (outside the pelvic area) and found significantly lower SUVs with OSEM-MAC [16]. All these studies differed both from each other and from the present study in at least one aspect (image acquisition, number of iterations and subsets, filtering and the method of attenuation correction), which could explain the conflicting results. In the present study, $SUV_{[FBP]}$ and $SUV_{[OSEM]}$ were comparable (Table 2), but a limitation of these results is that measurements were interdependent, because the same ROIs (drawn on OSEM images)

had to be used for calculation of $SUV_{[OSEM}$ and $SUV_{[FBP]}$. This was related to the distinct disadvantages of FBP images compared with OSEM (streak artefacts, inferior lesion detectability and noisier images, especially with low FDG uptake), making reliable ROI definition possible only on OSEM reconstructed images.

Conclusion

The method of ROI definition has a direct influence on quantitative outcome. In terms of simplicity, user-independence, reproducibility and general applicability, the threshold-based and fixed dimension methods are the best ROI methods. Threshold methods are in addition relatively independent of changes in size and geometry, however, and may therefore be more suitable for response monitoring purposes. When measuring relative changes in FDG uptake, all SUVs show the same trend, regardless of the ROI method used.

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